Monday, August 22, 2016

PCB Assessment Team Meeting – MINUTES

In attendance: Geniece, Jenny, Evan, Laura, Danelle, Xabier, April, Anu, Marian, Paul, Mike, Michael, Swati, ICF (Joanne Trgovcich, Allison Killius, Anna Engstrom), External Experts (Michael Bloom, Todd Jusko, Alexander Sergeev, Michal Toborek)

Due dates provided in these minutes have been updated to reflect delivery of hazard id reference lists to section authors on 8/25/16 (instead of the anticipated date, which was 8/22/16)

ICF STATUS UPDATE

- Ongoing: Develop draft mixtures modeling tool (due)
- Ongoing: screen and categorize hazard id references from literature search update (summer 2015 – summer 2016) (due 9/16/2016)
- Ongoing: ADME-specific literature search and screen (due 9/17/2016)
    - o Hazard id references containing ADME information have been incorporated into the ADME literature search and screen.
    - o We are currently evaluating methods for screening references in less-relevant reference clusters (as identified by machine learning/natural language processing).
    - o To evaluate the instructions for the 2nd step of the ADME literature screen, ICF will send Paul Schlosser preliminary screening results (the first 20-30 references screened), and based on the categorization of those studies, Paul will recommend edits to the screening instructions, if necessary.
- Ongoing: Literature search and screen for MOA studies (due 11/8/2016)

TEAM MEMBER UPDATES

- Please check the "[HYPERLINK "https://usepa-

Ex. 6 Personal Privacy (PP)

  scheduling updates.
- Team epidemiologists and toxicologists
    - o Overview of preliminary analysis plans and literature inventories:
        - The preliminary analysis plan will be the plan for extracting information into the inventory.
        - All studies in your reference lists will be listed in your inventory, but the amount of information extracted for each study will vary based on your preliminary analysis plan.
        - The preliminary analysis plans are due on 9/24/2016. We will discuss them at our team meeting on 9/26/2016 to make sure that everyone is on target to develop a useful inventory.
        - The inventories are due on 10/24/2016.
        - Details important for developing a preliminary plan and literature inventory are described below.
    - o Preliminary analysis plans (due 9/24/2016; to be discussed at team meeting on 9/26/2016)
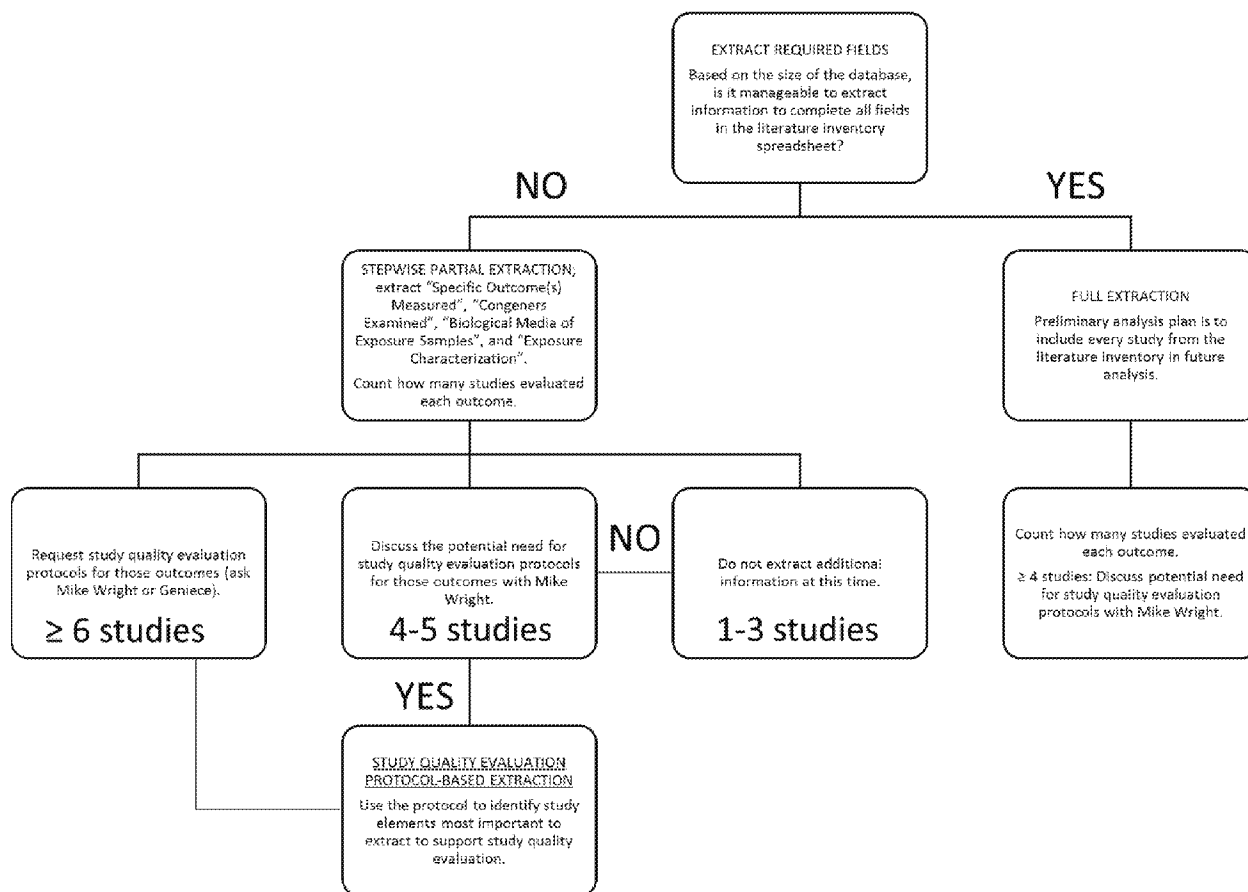
- **Human study databases**: Excel inventory; incomplete, but annotated with notes to indicate the following:
  - Which studies were excluded based on PECO considerations
    - Add a column to the inventory for notes to justify study exclusion
    - Common examples of PECO considerations are provided in the minutes from our 8/15/16 team meeting – PCB Assessment Team > Team Meeting Agendas & Minutes > 081516 – Preliminary Analysis Plans > [HYPERLINK "https://usepa-

Ex. 6 Personal Privacy (PP)

  - **New Example:** The PECO exposure criteria require that studies were conducted in humans exposed to PCBs and that their exposure to PCBs can be assessed separately from their exposure to other chemicals. Examples of study designs that fail to meet this criterion:
    - Studies in which the only exposure metric combines measures of PCBs with other chemicals (e.g., CALUX assay (measures "dioxin-like" activity and is a combined measure of dioxin-like PCBs and other dioxin-like compounds); sum of serum PCDD and PCB concentrations without any analysis for PCBs alone)
    - Yusho/Yu-Cheng studies in which the entire exposure assessment is based on study participants' status as a Yusho or Yu-Cheng patient (i.e., no measurement of PCBs in serum or other matrices)
    - Studies in which the entire exposure assessment is based on consumption of PCB-contaminated fish or other wildlife (i.e., no measurement of PCBs in the fish or in serum (or other samples) from the study participants)
    - An exception is occupational studies in which the entire exposure assessment is based on the identification of study participants as workers with a particular job function (i.e., no measurement of PCBs in the work environment or in serum (or other samples) from the study participants). These studies will be included at this stage because the magnitude of the difference in exposure between individuals who are occupationally exposed and those who are not is likely to be particularly high. Also, occupational exposure provides information on humans exposed to PCBs by the dermal and inhalation exposure routes. The inhalation exposure route is of particular interest for this assessment, and outside of occupational studies, there are very few examples of studies in humans where PCB inhalation exposure was evaluated.
  - May also exclude studies if they are conference abstracts or foreign language papers
  - No exclusions for study quality considerations – yet
    - Low-quality studies may be deprioritized following study quality evaluation
- Which studies will be fully extracted into the inventory
- Which study quality evaluation protocols have been requested
- Which studies will be partially extracted based on information most important for study quality evaluation, and which fields will be extracted for those studies

- Corrections have been made to the decision tree for determining preliminary analysis plans for human study databases (Figure 1). Please use this version instead of the one found in the minutes from our 8/15/16 team meeting.
    - All preliminary analysis plans should indicate that fields related to exposure assessment (i.e., "Congeners Examined", "Biological Media of Exposure Samples", and "Exposure Characterization") will be extracted (in addition to the "Specific Outcome(s) Measured" field). These are important for evaluating the quality of the exposure assessment in each study.
    - Previously, for health outcomes measured in 1-3 studies (i.e., those health outcomes not requiring an outcome-specific study quality evaluation protocol), you were asked to follow the guidelines for "FULL EXTRACTION". After further consideration, it doesn't seem like that is really necessary at this stage in the process. The quality of the exposure assessment methods used in those studies will be evaluated, and for that, we will need the information in the fields related to exposure assessment (see above). So, those fields should be extracted. However, other fields do not have to be extracted at this time for studies evaluating health outcomes that were measured in only 1-3 studies.
    - The previous decision tree did not make it clear that authors with small databases (where the preliminary analysis plan is to extract information fully for all studies) should also identify health outcomes for which study quality evaluation protocols will be needed.

Figure [SEQ Figure * ARABIC]. CORRECTED Decision Tree to Determine Preliminary Analysis Plans for Human Study Databases

- **Animal study databases**: Excel inventory; incomplete, but annotated with notes to indicate the following:
  - Which studies were excluded based on PECO considerations
    - Common examples of PECO considerations are provided in the minutes from our 8/15/16 team meeting – PCB Assessment Team > Team Meeting Agendas & Minutes > 081516 – Preliminary Analysis Plans > [HYPERLINK "https://usepa-

Ex. 6 Personal Privacy (PP)

  - May also exclude studies if they are conference abstracts or foreign language papers
  - Which studies will be fully extracted into the inventory
    - Make this determination based on the size of the database for each test compound (i.e., each PCB mixture or individual congener) administered.
  - Which studies will not be fully extracted because they do not meet the following criteria:
    - Administered PCBs by the oral, inhalation, or dermal exposure route OR evaluated outcomes resulting from developmental exposure

- o Administered PCBs over a chronic or subchronic duration OR evaluated outcomes resulting from developmental exposure
- o Evaluated under-studied outcomes
  - Studies evaluating under-studied outcomes may be fully extracted regardless of the exposure route or duration utilized by the study, especially if the outcomes are strong indicators of health hazard or if they are shown to occur at relatively low levels of PCB exposure.
- o Literature inventories (due 10/24/2016)
  - Excel inventory; completed in accordance with preliminary analysis plan
- o Study quality evaluation protocols
  - Protocols will include information on which study designs and which exposure and outcome assessment methods are more or less reliable.
  - Protocols will be made publicly available and the assessment will describe the use of each protocol in making decisions regarding which studies to consider more or less informative.
  - Human study databases
    - Outcome-specific protocols developed through IRIS epidemiology WG (due 11/23/2016)
    - Protocol to evaluate quality of PCB exposure assessment in human studies (due 11/23/2016)
      - o Contributors:
        - PCB team epidemiologists
      - o Reviewers:
        - IRIS epidemiology WG
      - o The planned approach is to use the protocol from the phthalates assessments as a template, adding in information specific for PCBs.
        - Information in the "Congeners Examined", "Biological Media of Exposure Samples", and "Exposure Characterization" fields of the literature inventories can be collected to support the development of the study quality evaluation protocol.
  - Animal study databases
    - General protocol to apply to animal toxicology studies (due 10/24/2016)
      - o Path forward is unclear; possible contributors:
        - IRIS systematic review WG
        - IRIS neurological, reproductive, and developmental toxicology WG
        - PCB team toxicologists
      - o Reviewers
        - IRIS systematic review WG
        - IRIS general toxicology WG
        - IRIS neurological, reproductive, and developmental toxicology WG
        - PCB team toxicologists
    - Outcome-specific protocols developed by modifying and refining the general protocol to incorporate information on factors that can influence the evaluation of specific endpoints (due 11/23/2016)

- The PCB team will continue to work collaboratively to develop a protocol for evaluating the quality of oral exposure methods used in animal toxicology studies of PCBs (due 10/24/16).
  - Evidence table reviews (ongoing; as requested)
- ADME and PK modeling
  - First products due 11/16/2016
    - ADME literature inventory
    - Data extraction protocol for ADME studies
    - What support is needed from other team members?
      - For discussion at our team meeting on 9/19

UPCOMING

- Webinar series
  - (August 25) Effects on social and behavioral responses (Ross Gillette and Michael Reilly)
- Team meetings (suggestions for meeting topics are welcome)
  - (August 29) Study quality evaluation protocols
  - (September 12) MOA check-in
    - Jenny Li will review the anticipated approach to developing MOA analyses
    - Remind team toxicologists to take note of MOA evidence to support future development of PECO statements and search strings
  - (September 19) ADME check-in
    - How can team epidemiologists and toxicologists support ADME literature inventory and data extraction protocol development?
  - (September 26) Preliminary analysis plan check-in
    - At this meeting, we will also discuss health effects in our literature inventories that may be candidates for economic analysis
  - (October 17) Data Extraction Protocols
    - Gather available information and resources to support data extraction protocol development
    - Review of data extraction requirements for BMD and CatReg analyses
    - Ensure consistent dose conversion across tox sections
  - (October 24) ADME check-in
  - (October 31) Study quality evaluations (how to use the protocols)
  - (November 7) Discuss feedback on sample evidence tables
  - (November 14) Susceptibility considerations
  - (November 21) MOA check-in
    - Meet to discuss proposed PECO statements and search strings with information specialists from HERO and ICF